

AperTO - Archivio Istituzionale Open Access dell'Università di Torino

Understanding the effects of air pollution on neurogenesis and gliogenesis in the growing and adult brain

This is the author's manuscript

Original Citation:

Availability:

This version is available <http://hdl.handle.net/2318/1727123> since 2020-02-10T00:05:11Z

Published version:

DOI:10.1016/j.coph.2019.12.003

Terms of use:

Open Access

Anyone can freely access the full text of works made available as "Open Access". Works made available under a Creative Commons license can be used according to the terms and conditions of said license. Use of all other works requires consent of the right holder (author or publisher) if not exempted from copyright protection by the applicable law.

(Article begins on next page)

1 **Understanding the effects of air pollution on neurogenesis and gliogenesis in the**
2 **growing and adult brain**

3 **Enrica Boda^{1,2*}, Antonello E. Rigamonti³, Valentina Bollati³**

4

5 *Affiliations:*

6 ¹ Department of Neuroscience Rita Levi-Montalcini, University of Turin

7 ² Neuroscience Institute Cavalieri Ottolenghi (NICO), University of Turin, Regione Gonzole,
8 10 – 10043 Orbassano (Turin), Italy

9 ³Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy

10

11 ** Corresponding author:*

12 Enrica Boda

13 Neuroscience Institute Cavalieri Ottolenghi (NICO), University of Turin, Regione Gonzole,
14 10 – 10043 Orbassano (Turin), Italy

15 enrica.boda@unito.it

16

17 **Abstract**

18 Exposure to air pollution – and particularly to particulate matter (PM) – is strongly
19 associated with higher risk of neurodevelopmental disorders, poor mental health and
20 cognitive defects. In animal models, disruption of CNS development and disturbances of
21 adult neurogenesis contribute to PM neurotoxicity. Recent studies show that gestational
22 PM exposure not only affects embryonic neurodevelopment, but also disturbs postnatal
23 brain growth and maturation, by interfering with neurogenic/gliogenic events, myelination
24 and synaptogenesis. Similarly, adult neurogenesis is affected at many levels, from neural
25 stem cell amplification up to the maturation and integration of novel neurons in the adult
26 brain parenchyma. The underlying mechanisms are still by and large unknown. Beyond
27 microglia activation and neuroinflammation, recent studies propose a role for novel
28 epigenetic mechanisms, including DNA methylation and extracellular vesicles-associated
29 microRNAs.

30 Exposure to air pollution is increasingly acknowledged as one of the main contributors to
31 the global disease burden [1]. It has been estimated that in 2016 91% of the world
32 population was living in places where the WHO air quality guidelines levels were not met
33 ([https://www.who.int/news-room/fact-sheets/detail/ambient-\(outdoor\)-air-quality-and-](https://www.who.int/news-room/fact-sheets/detail/ambient-(outdoor)-air-quality-and-health)
34 [health](https://www.who.int/news-room/fact-sheets/detail/ambient-(outdoor)-air-quality-and-health)). Among the key air pollutants that pose health risks, particulate matter (PM) is one
35 of the most widespread. PM is a heterogeneous mixture of small solid or liquid particles
36 released into the atmosphere during combustion processes or emitted by industrial
37 activities and natural sources. PM generally comprises water soluble and insoluble
38 components, including inorganic compounds, polycyclic aromatic hydrocarbons, heavy
39 metals and other toxic substances, and microbial components, such as bacteria and their
40 products of degradation (e.g. lipopolysaccharide) and viruses [2]. PM is defined according
41 to its aerodynamic diameter, with coarse PM smaller than 10 μm (PM_{10}) and fine and
42 ultrafine PM smaller than 2.5 ($\text{PM}_{2.5}$) or 0.1 ($\text{PM}_{0.1}$) μm , respectively. Thanks to their small
43 size, when inhaled, PM particles have the capability to percolate through the respiratory
44 tract. While PM_{10} is trapped in the upper airways, $\text{PM}_{2.5}$ reaches the lungs and deposits in
45 the alveolar area. Ultrafine particles could even penetrate into the blood circulation and
46 overcome the blood-brain-barrier (BBB) [3,4], or pass through the nasal mucosa and
47 directly enter the brain [5,6]. Of note, inhaled nanoparticles have been shown to cross the
48 placental barrier and to deposit in the fetal tissues in animal models [7], suggesting a
49 possible mother-to-fetus transfer of airborne ultrafine PM.

50 Chronic exposure to air pollution has been consistently associated with risk of
51 cardiovascular and respiratory diseases, and different types of cancer [1]. Increasing
52 evidence also indicates that the central nervous system (CNS) is a target for air pollution.
53 In utero and early child exposure to high levels of air pollution, and in particular to PM, is
54 associated with higher risk of neurodevelopmental disorders, long-lasting behavioral
55 alterations and cognitive defects [8,9]. Moreover, during adulthood, chronic PM exposure

56 has been associated with poor mental health, increased risk of onset and worsening of
57 depression [9], while both short and long term exposure has been associated with
58 cognitive/memory deterioration [10,11].

59 Most studies in animal models that aimed at establishing a causative link between air
60 pollution and anatomical/functional CNS alterations, and at unveiling the underlying
61 mechanisms, are focused on the effects of PM. In rodents, PM exposure results in
62 neurodevelopmental, cognitive and behavioral alterations reminiscent of those observed in
63 humans, whose extent and duration depend on PM size, doses and timing of exposure
64 [12–17]. Mechanistically, disruption of CNS development and of adult neurogenesis were
65 found to contribute to PM detrimental effects, suggesting the occurrence of similar events
66 in humans.

67 In this review, we summarize recent advancements toward the understanding of the
68 cellular and molecular mechanisms mediating PM effects on the developmental and adult
69 neurogenesis and gliogenesis, discuss limitations of the available studies and highlight
70 persisting open issues.

71

72 **In utero and neonatal exposure to PM induces neurodevelopmental alterations in** 73 **animal models**

74 In mice, chronic prenatal exposure to high levels of fine and ultrafine PM was reportedly
75 associated with reduced brain weight and ventriculomegaly at birth and during the first
76 postnatal period [13,18]. This is the outcome of the disruption of specific and diverse
77 neurodevelopmental events. Exposure to diesel exhaust particles (DEP) in mouse
78 pregnant dams throughout gestation resulted, in the offspring, in increased cortical (i.e.
79 prefrontal cortex) and hippocampal (i.e. dentate gyrus, DG) volumes at embryonic day
80 (E)18, which switched to decreased cortical volume and normalized hippocampal size in
81 postnatal day (P)30 males (but not in females), compared to untreated animals [19].

82 Similarly, maternal inhalation of carbon black nanoparticles (produced by the incomplete
83 combustion of petroleum products) resulted in an initial increase of parvalbumin-positive
84 (+) neurons in the uppermost layers of the motor cortex, followed by a large reduction at
85 later time points [20]. These results suggest that gestational PM exposure may
86 differentially affect distinct phases of brain development and cause an initial tissue
87 overgrowth – possibly due to neural stem cell (NSC)/progenitor over-expansion - followed
88 by postnatal regressive events. Thus, the effects on CNS development of in utero PM
89 exposure can be persistent and extend beyond the embryonic period. In line with this
90 interpretation, two recent studies [12,21] have shown that chronic prenatal exposure to
91 high dosages of PM_{2.5} resulted in increased neuronal and astrocyte apoptosis in the cortex
92 and distinct hippocampal subregions, including the DG, of the offspring at P14-P30.
93 Postnatal hippocampal neurogenesis and astrogliogenesis appeared also dramatically
94 reduced, due to the suppression of NSC proliferation in the subgranular zone (SGZ).
95 Similarly, parenchymal astro- and oligo-dendroglia amplification was affected, as indirectly
96 assessed by the large decrease of the proliferation marker PCNA in the cortex of P1-P30
97 offspring [21]. In agreement with this finding, gestational chronic exposure to fine and
98 ultrafine particles has been associated with precocious myelination and premature
99 oligodendroglia proliferation/differentiation switch in the corpus callosum of the adolescent
100 offspring [13,22]. Dendritic complexity [15] and number of asymmetric excitatory synapses
101 impinging on hippocampal neurons were also significantly reduced in adolescent (P14)
102 mice prenatally exposed to PM_{2.5}. The remaining synapses showed altered -and possibly
103 compensatory- features, including increased number of presynaptic vesicles, thickened
104 postsynaptic density and decreased synaptic space [12].

105 Thus, gestational PM exposure not only affects embryonic neurodevelopment, but also
106 disturbs postnatal brain growth and maturation, by interfering with neurogenic/gliogenic
107 events, myelination and synaptogenesis. Pregnancy appears to be a particularly

108 vulnerable time window, since neonatal exposure had milder effects, and mostly affected
109 myelination [23,24] and expression of synaptic proteins [14].

110 111 **PM exposure disturbs adult neurogenesis in animal models**

112 In the adult mouse brain, generation of new neurons continues in the subventricular zone
113 (SVZ) of the lateral ventricles and in the SGZ of the hippocampus [25]. Adult neurogenesis
114 in the SVZ cannot be detected in humans, whereas controversial evidence has been
115 provided about the generation of new neurons in the adult human hippocampus [26–28].
116 Thus, while adult hippocampal neurogenesis is implicated in cognitive processes and
117 mood regulation in rodents [29], whether this occurs also in adult humans is highly
118 debated. Nevertheless, adult neurogenesis in rodents recapitulates many aspects of the
119 developmental neurogenic/gliogenic events. Therefore, the study of the mechanisms
120 mediating PM-induced perturbations of the adult neurogenic niches is still of interest, as it
121 can unveil critical toxicity processes operating in both developing and mature CNS.

122 In a recent study, acute exposure to fine DEP caused an impairment of adult neurogenesis
123 in mice. This effect was gender-specific, with males showing fewer newly-generated
124 neurons in SGZ, SVZ and olfactory bulb (OB), compared to control animals, and females
125 displaying fewer new neurons only in the OB [30]. Reduced neurogenesis was a
126 consequence of decreased proliferation of NSCs/progenitors, reduced survival of
127 immature neurons, and altered specification/differentiation of newborn elements (i.e.
128 reduced fraction of newborn cells expressing the mature neuronal marker NeuN 3 weeks
129 after their generation [30]). Moreover, life-long exposure to concentrated water-soluble
130 subfraction of PM_{0.2} dramatically reduced the number of SGZ newborn neurons -but not of
131 newborn astrocytes- in adult male rats, which also showed contextual memory defects and
132 depressive behaviors [16]. Thus, PM appears to negatively modulate the neurogenic
133 events at many levels, from NSCs division up to the maturation and integration of novel

134 neurons in the adult brain parenchyma. In line with this view, chronic inhalation of
135 ammonium sulfate, the major inorganic component in PM_{2.5} (as resulting from the reaction
136 of ammonia, mostly originating from animal farming and synthetic fertilizers, with sulfur
137 dioxide emitted by the burning of fossil fuels [31]), diminished the dendritic complexity of
138 immature neurons in the DG of aged rats [32]. However, in this latter study, no alteration of
139 SGZ/SVZ NSC/progenitor proliferation and of the specification of their derivatives could be
140 detected, highlighting a specific neurotoxicity of the distinct components of PM.

141

142 **Proposed mechanisms underlying the effects of PM on neurogenesis and** 143 **gliogenesis**

144 In rodents, neuroinflammation accompanied by microglia and astrocyte activation were
145 cardinal effects of PM exposure, whenever it occurs [12–16,19,20,23,24,30].
146 Pharmacological treatments aimed at blocking microglia polarization – such as the
147 peroxisome proliferator-activated receptor γ (PPAR γ) agonist pioglitazone - protected
148 against PM-induced suppression of SGZ proliferation and rescued the number of newborn
149 neurons, indicating a major role of microglia reactivity in the negative modulation of adult
150 hippocampal neurogenesis [30]. Nevertheless, mechanistically, which activated microglia
151 phenotype (i.e. proregenerative M2 vs. neurotoxic M1 vs. “dark microglia” [33]) is favored
152 upon/after PM exposure and how microglia activation inhibits the neurogenic events
153 remain obscure. Beyond the release of high levels of pro-inflammatory cytokines or
154 reactive oxygen species, that can inhibit NSC/progenitor proliferation and alter the
155 specification and survival of their derivatives [34], an interesting hypothesis is that PM-
156 induced microglia activation could result in increased phagoptosis (i.e. the engulfment of
157 immature viable neurons [35]). In line with this hypothesis, Bolton and colleagues [19]
158 reported increased microglia-neuron physical interactions in the cortex of the offspring of
159 PM-exposed dams.

160 Notably, upon prenatal and neonatal PM exposure, microglia activation and astrogliosis
161 occurred predominantly in males [19,23,24,36]. Consistently, neuroinflammation was more
162 pronounced in males than in females upon exposure to DEP during adulthood [37], in line
163 with a more marked reduction of adult neurogenesis [30]. This suggests that sex-
164 dependent factors, including the hormonal background, may influence the individual's
165 vulnerability to PM effects. Interestingly, microglia activation and neuroinflammation
166 extended well beyond PM-exposure, when it occurred in utero, in line with a priming action
167 of air pollution.

168 Moreover, what is the trigger for microglia and astrocyte activation remains elusive. Fine
169 and ultrafine particles could enter the CNS and directly stimulate glial reactivity. Given the
170 relatively small extension of the olfactory mucosa, it is likely that in humans – at difference
171 with rodents - the main entrance route for PM is the blood. In line with this view, astroglia
172 reactivity was observed predominantly around blood vessels [38]. Nevertheless, glial cells
173 and NSCs/progenitors may be reached by a plethora of other factors – and even cells-
174 from the periphery, thanks to the disruption of BBB integrity and increased leakage
175 induced by PM exposure [13,16]. Among these elements, pulmonary cell-derived
176 extracellular vesicles (EVs) may represent important lung-to-brain mediators of PM effects
177 [39,40]. EVs are lipid bilayer-delimited particles, actively released from cells in response to
178 stress. After internalization within target cells, EVs deliver their content, including proteins,
179 lipids and miRNAs, and profoundly influence the recipient cell molecular state and function
180 [41]. Interestingly, recent studies [39,40] showed that, in humans, the miRNA cargo of
181 plasma EVs released following PM exposure has a signature relevant for the modulation of
182 glial cell reactivity (e.g. miR-9, involved in microglia activation and neuroinflammation [42])
183 and NSC/progenitor functions (e.g. miR-128, miR-302, let-7 and miR-9, regulating neural
184 precursor proliferation and neurogenesis [43]; miR-21, miR-9, miR-200, miR-17, miR-7,
185 miR-302c, limiting oligodendroglia differentiation or enriched in immature oligodendrocyte

precursors [44]). Finally, a novel epigenetic mechanism possibly mediating PM effects on developmental and adult neurogenesis may be the regulation of DNA methylation in NSCs and their derivatives, that has been shown to be responsive to extrinsic signals and to influence multiple aspects of neurogenesis from stem cell maintenance up to synaptogenesis [45]. This hypothesis is corroborated by the observation of increased DNA methyltransferase DNMT1 in the brains of male mice perinatally exposed to DEP [46]. Notably, in human placenta, PM exposure was associated with altered methylation level of DNA repair and clock genes [47,48], which are also essential for adult and developmental neurogenesis [49–51].

195

196 **Concluding remarks and open issues**

Convincing evidence, obtained in animal models, shows that CNS development and adult neurogenesis are profoundly impacted by PM exposure throughout life, with significant behavioral and cognitive alterations. This field of research is still in its infancy and strenuous efforts are still needed to clarify the precise mechanisms by which PM affects neurodevelopmental events and adult neurogenesis, and the molecular substrates of gender and time window -specific differences in PM sensitivity. Available mechanistic studies have frequently exploited heterogeneous PM dosages, composition, administration modalities and timing. This scenario has so far impeded a complete understanding of the processes subserving PM effects. Nevertheless, research on the effects of PM on other systems has greatly advanced in the last years and identified interesting candidate mechanisms that could be also at the basis of PM neurotoxicity.

208 **References**

- 209 1. Stanaway JD, Afshin A, Gakidou E, Lim SS, Abate D, Abate KH, Abbafati C, Abbasi
210 N, Abbastabar H, Abd-Allah F, et al.: **Global, regional, and national comparative**
211 **risk assessment of 84 behavioural, environmental and occupational, and**
212 **metabolic risks or clusters of risks for 195 countries and territories, 1990-**
213 **2017: A systematic analysis for the Global Burden of Disease Study 2017.**
214 *Lancet* 2018, **392**:1923-1994.
- 215 2. Becker S, Fenton MJ, Soukup JM: **Involvement of microbial components and**
216 **toll-like receptors 2 and 4 in cytokine responses to air pollution particles.** *Am J*
217 *Respir Cell Mol Biol* 2002, **27**:611-618.
- 218 3. Nemmar A, Hoet PHM, Vanquickenborne B, Dinsdale D, Thomeer M, Hoylaerts MF,
219 Vanbilloen H, Mortelmans L, Nemery B: **Passage of inhaled particles into the**
220 **blood circulation in humans.** *Circulation* 2002, **105**:411-414.
- 221 4. Li D, Li Y, Li G, Zhang Y, Li J, Chen H: **Fluorescent reconstitution on deposition**
222 **of PM 2.5 in lung and extrapulmonary organs.** *Proc Natl Acad Sci U S A* 2019,
223 **116**:2488–2493. * *Using a novel fluorescence imaging method, the authors show the*
224 *distribution of (even single particles) PM2.5 in extrapulmonary organs with a high*
225 *temporal and spatial resolution.*
- 226 5. Oberdörster G, Sharp Z, Atudorei V, Elder A, Gelein R, Kreyling W, Cox C:
227 **Translocation of inhaled ultrafine particles to the brain.** *Inhalation Toxicology*
228 2004, **16**:437-445.
- 229 6. Maher BA, Ahmed IAM, Karloukovski V, MacLaren DA, Foulds PG, Allsop D, Mann
230 DMA, Torres-Jardón R, Calderon-Garciduenas L: **Magnetite pollution**
231 **nanoparticles in the human brain.** *Proc Natl Acad Sci U S A* 2016, **113**:10797–
232 10801.
- 233 7. Campagnolo L, Massimiani M, Vecchione L, Piccirilli D, Toschi N, Magrini A,

- Bonanno E, Scimeca M, Castagnozzi L, Buonanno G, et al.: **Silver nanoparticles inhaled during pregnancy reach and affect the placenta and the fetus.** *Nanotoxicology* 2017, **11**:687–698. * *By means of transmission electron microscopy coupled with energy-dispersive X-ray spectroscopy and single-particle inductively coupled plasma mass spectrometry, the authors analyze the distribution of inhaled silver nanoparticles in maternal tissues and in the fetus. This is one of the few direct demonstrations that, in animal models, inhaled nanoparticles can reach the placenta and the fetus.*
8. Woodward N, E. Finch C, E. Morgan T: **Traffic-related air pollution and brain development.** *AIMS Environ Sci* 2015, **2**:353–373.
9. Buoli M, Grassi S, Caldiroli A, Carnevali GS, Mucci F, Iodice S, Cantone L, Pergoli L, Bollati V: **Is there a link between air pollution and mental disorders?** *Environ Int* 2018, **118**:154–168.
10. Zhang X, Chen X, Zhang X: **The impact of exposure to air pollution on cognitive performance.** *Proc Natl Acad Sci U S A* 2018, **115**:9193–9197. ** *By matching a longitudinal survey and air quality data in China, the authors examine the effect of both cumulative and acute exposures to air pollution for the same individuals over time on cognitive performance. They provide a well-documented demonstration that chronic exposure to air pollution impedes cognitive performance in verbal and math tests, and identify most vulnerable population cohorts.*
11. Shehab MA, Pope FD: **Effects of short-term exposure to particulate matter air pollution on cognitive performance.** *Sci Rep* 2019, **9**:1–10.
12. Zheng X, Wang X, Wang T, Zhang H, Wu H, Zhang C, Yu L, Guan Y: **Gestational exposure to particulate matter 2.5 (PM 2.5) leads to spatial memory dysfunction and neurodevelopmental impairment in hippocampus of mice offspring.** *Front Neurosci* 2019, **13**:1–18.

- 260 13. Klocke C, Allen JL, Sobolewski M, Mayer-Pröschel M, Blum JL, Lauterstein D,
261 Zelikoff JT, Cory-Slechta DA: **Neuropathological consequences of gestational**
262 **exposure to concentrated ambient fine and ultrafine particles in the mouse.**
263 *Toxicol Sci* 2017, **156**:492–508.
- 264 14. Li K, Li L, Cui B, Gai Z, Li Q, Wang S, Yan J, Lin B, Tian L, Liu H, et al.: **Early**
265 **Postnatal Exposure to Airborne Fine Particulate Matter Induces Autism-like**
266 **Phenotypes in Male Rats.** *Toxicol Sci* 2018, **162**:189–199.
- 267 15. Tseng CY, Yu JY, Chuang YC, Lin CY, Wu CH, Liao CW, Yang FH, Chao MW: **The**
268 **Effect of Ganoderma Microsporum immunomodulatory proteins on alleviating**
269 **PM 2.5 -induced inflammatory responses in pregnant rats and fine particulate**
270 **matter-induced neurological damage in the offsprings.** *Sci Rep* 2019, **9**:1–10.
- 271 16. Woodward NC, Haghani A, Johnson RG, Hsu TM, Saffari A, Sioutas C, Kanoski SE,
272 Finch CE, Morgan TE: **Prenatal and early life exposure to air pollution induced**
273 **hippocampal vascular leakage and impaired neurogenesis in association with**
274 **behavioral deficits.** *Transl Psychiatry* 2018, **8**:1–10. * *The authors show that, in*
275 *rats, in utero and early life exposure to air pollution is associated with impaired*
276 *contextual memory (novel object in context), reduced food-seeking behavior, and*
277 *increased depressive behaviors (forced swim) at adult stages. This is accompanied*
278 *by BBB breakdown and decreased numbers of newly generated neurons in the DG.*
- 279 17. Fonken LK, Xu X, Weil ZM, Chen G, Sun Q, Rajagopalan S, Nelson RJ: **Air**
280 **pollution impairs cognition, provokes depressive-like behaviors and alters**
281 **hippocampal cytokine expression and morphology.** *Mol Psychiatry* 2011,
282 **16**:987–995.
- 283 18. Wu G, Brown J, Zamora ML, Miller A, Satterfield MC, Meininger CJ, Steinhauser CB,
284 Johnson GA, Burghardt RC, Bazer FW, et al.: **Adverse organogenesis and**
285 **predisposed long-term metabolic syndrome from prenatal exposure to fine**

particulate matter. *Proc Natl Acad Sci U S A* 2019, **116**:11590–11595.

19. Bolton JL, Marinero S, Hassanzadeh T, Natesan D, Le D, Belliveau C, Mason SN, Auten RL, Bilbo SD: **Gestational exposure to air pollution alters cortical volume, microglial morphology, and microglia-neuron interactions in a sex-specific manner.** *Front Synaptic Neurosci* 2017, **9**:1–16. * *By analyzing mice prenatally exposed to DEP, the authors show an initial over-expansion of the cortex at late embryonic ages, which switched to decreased volume in young adult males. They also find increased microglial-neuronal interactions in DEP-exposed male offspring compared to other groups, suggesting that microglia activation mediates PM effects on brain growth.*

20. Umezawa M, Onoda A, Korshunova I, Jensen ACØ, Koponen IK, Jensen KA, Khodosevich K, Vogel U, Hougaard KS: **Maternal inhalation of carbon black nanoparticles induces neurodevelopmental changes in mouse offspring.** *Part Fibre Toxicol* 2018, **15**:36.

21. Zhang T, Zheng X, Wang X, Zhao H, Wang T, Zhang H, Li W, Shen H, Yu L: **Maternal exposure to PM 2.5 during pregnancy induces impaired development of cerebral cortex in mice offspring.** *Int J Mol Sci* 2018, **19**: pii:E257.

22. Klocke C, Allen JL, Sobolewski M, Blum JL, Zelikoff JT, Cory-Slechta DA: **Exposure to fine and ultrafine particulate matter during gestation alters postnatal oligodendrocyte maturation, proliferation capacity, and myelination.** *Neurotoxicology* 2018, **65**:196–206.* *This paper shows that in utero exposure to fine and ultrafine PM in mouse results in persistent hypermyelination of the corpus callosum, due to the precocious engagement of oligodendroglia precursors into maturation, at the expenses of the amplification phase.*

23. Allen JL, Oberdorster G, Morris-Schaffer K, Wong C, Klocke C, Sobolewski M, Conrad K, Mayer-Proschel M, Cory-Slechta DA: **Developmental neurotoxicity of**

inhaled ambient ultrafine particle air pollution: Parallels with neuropathological and behavioral features of autism and other neurodevelopmental disorders. *Neurotoxicology* 2017, **59**:140–154.

24. Morris-Schaffer K, Merrill AK, Wong C, Jew K, Sobolewski M, Cory-Slechta DA: **Limited developmental neurotoxicity from neonatal inhalation exposure to diesel exhaust particles in C57BL/6 mice.** *Part Fibre Toxicol* 2019, **16**:1–14.

25. Obernier K, Alvarez-Buylla A: **Neural stem cells: Origin, heterogeneity and regulation in the adult mammalian brain.** *Development* 2019, **146**: pii: dev156059.

26. Moreno-Jiménez EP, Flor-García M, Terreros-Roncal J, Rábano A, Cafini F, Pallas-Bazarra N, Ávila J, Llorens-Martín M: **Adult hippocampal neurogenesis is abundant in neurologically healthy subjects and drops sharply in patients with Alzheimer's disease.** *Nat Med* 2019, **25**:554-560. *** By analyzing human brain samples obtained under tightly controlled conditions, the authors show an abundant population of neuroblasts in the DG of neurologically healthy human subjects up to the ninth decade of life. This is one of the most recent papers describing the presence of immature neurons in the adult hippocampus, although the authors do not demonstrate that these neurons are generated during the adult life.*

27. Sorrells SF, Paredes MF, Cebrian-Silla A, Sandoval K, Qi D, Kelley KW, James D, Mayer S, Chang J, Augustine KI, et al.: **Human hippocampal neurogenesis drops sharply in children to undetectable levels in adults.** *Nature* 2018, **555**:377-381. *** By analyzing the DG of human subjects at different ages, the authors show that the number of proliferating progenitors and young neurons declines sharply during the first year of life and only a few isolated young neurons persist by 7 and 13 years of age. In adult healthy adults, young neurons cannot be detected in the DG. Similar findings are obtained in the monkey hippocampus. Results of this paper support the view that adult hippocampal neurogenesis does not occur in humans.*

- 338 28. Boldrini M, Fulmore CA, Tartt AN, Simeon LR, Pavlova I, Poposka V, Rosoklija GB,
339 Stankov A, Arango V, Dwork AJ, et al.: **Human Hippocampal Neurogenesis**
340 **Persists throughout Aging.** *Cell Stem Cell* 2018, **22**:589-599. ** *By analyzing*
341 *whole autopsy hippocampi from healthy (i.e. without cognitive impairment,*
342 *neuropsychiatric disease, or treatment) human individuals ranging from 14 to 79*
343 *years of age, the authors find an abundant and comparable population of*
344 *intermediate progenitors and of immature neurons in the DG of young and old*
345 *subjects, with equivalent DG volume across ages. Yet, older individuals have a*
346 *smaller quiescent progenitor pool. This is one of the most recent papers describing*
347 *the presence of immature neurons in the adult hippocampus, although the authors*
348 *do not demonstrate that these neurons are generated during the adult life.*
- 349 29. Anacker C, Hen R: **Adult hippocampal neurogenesis and cognitive flexibility-**
350 **linking memory and mood.** *Nat Rev Neurosci* 2017, **18**:335-346.
- 351 30. Coburn JL, Cole TB, Dao KT, Costa LG: **Acute exposure to diesel exhaust**
352 **impairs adult neurogenesis in mice: prominence in males and protective effect**
353 **of pioglitazone.** *Arch Toxicol* 2018, **92**:1815–1829. * *This paper provides a*
354 *characterization of DEP effects on adult neurogenesis in the mouse SVZ/OB system*
355 *and DG. The authors implicate microglia activation in these effects, since*
356 *pioglitazone protected against DEP-induced alterations of hippocampal*
357 *neurogenesis.*
- 358 31. Brunekreef B, Harrison RM, Künzli N, Querol X, Sutton MA, Heederik DJ, Sigsgaard
359 T. **Reducing the health effect of particles from agriculture.** *Lancet Respir Med*
360 2015, **3**:831-2.
- 361 32. Cheng L, Lau WKW, Fung TKH, Lau BWM, Chau BKH, Liang Y, Wang Z, So KF,
362 Wang T, Chan CCH, et al.: **PM2.5 Exposure Suppresses Dendritic Maturation in**
363 **Subgranular Zone in Aged Rats.** *Neurotox Res* 2017, **32**:50–57.

- 364 33. Bisht K, Sharma KP, Lecours C, Gabriela Sánchez M, El Hajj H, Milior G, Olmos-
365 Alonso A, Gómez-Nicola D, Luheshi G, Vallières L, et al.: **Dark microglia: A new**
366 **phenotype predominantly associated with pathological states.** *Glia* 2016,
367 **64**:826-839.
- 368 34. Rolando C, Boda E, Buffo A: **Immune system modulation of parenchymal and**
369 **germinal neural progenitor cells in physiological and pathological conditions.**
370 *In: Sun Tao. Neural Stem Cells and Therapy (InTech, ISBN: 9789533079585)* 2012,
371 413-440.
- 372 35. Brown GC, Neher JJ: **Microglial phagocytosis of live neurons.** *Nat Rev Neurosci*
373 2014, **15**:209-216.
- 374 36. Allen JL, Liu X, Weston D, Prince L, Oberdörster G, Finkelstein JN, Johnston CJ,
375 Cory-Slechta DA: **Developmental exposure to concentrated ambient ultrafine**
376 **particulate matter air pollution in mice results in persistent and sex-dependent**
377 **behavioral neurotoxicity and glial activation.** *Toxicol Sci* 2014, **140**:160–178.
- 378 37. Cole TB, Coburn J, Dao K, Roqué P, Chang YC, Kalia V, Guilarte TR, Dziedzic J,
379 Costa LG: **Sex and genetic differences in the effects of acute diesel exhaust**
380 **exposure on inflammation and oxidative stress in mouse brain.** *Toxicology*
381 2016, **374**:1-9.
- 382 38. Onoda A, Takeda K, Umezawa M: **Dose-dependent induction of astrocyte**
383 **activation and reactive astrogliosis in mouse brain following maternal**
384 **exposure to carbon black nanoparticle.** *Part Fibre Toxicol* 2017, **14**:1–16.
- 385 39. Pavanello S, Bonzini M, Angelici L, Motta V, Pergoli L, Hoxha M, Cantone L,
386 Pesatori AC, Apostoli P, Tripodi A, et al.: **Extracellular vesicle-driven information**
387 **mediates the long-term effects of particulate matter exposure on coagulation**
388 **and inflammation pathways.** *Toxicol Lett* 2016, **259**:143-150.
- 389 40. Pergoli L, Cantone L, Favero C, Angelici L, Iodice S, Pinatel E, Hoxha M, Dioni L,

Letizia M, Albetti B, et al.: **Extracellular vesicle-packaged miRNA release after short-term exposure to particulate matter is associated with increased coagulation.** *Part Fibre Toxicol* 2017, **14**:32.

41. Raposo G, Stoorvogel W: **Extracellular vesicles: Exosomes, microvesicles, and friends.** *J Cell Biol* 2013, **200**:373-83.

42. Yao H, Ma R, Yang L, Hu G, Chen X, Duan M, Kook Y, Niu F, Liao K, Fu M, et al.: **MiR-9 promotes microglial activation by targeting MCP1.** *Nat Commun* 2014, **5**:4386.

43. Kawahara H, Imai T, Okano H: **MicroRNAs in neural stem cells and neurogenesis.** *Front Neurosci* 2012, **6**:30.

44. Barca-Mayo O, Richard Lu Q: **Fine-tuning oligodendrocyte development by microRNAs.** *Front Neurosci* 2012, **6**:13.

45. Jobe EM, Zhao X: **DNA Methylation and Adult Neurogenesis.** *Brain Plast* 2016, **3**:5-26.

46. Chang YC, Daza R, Hevner R, Costa LG, Cole TB: **Prenatal and early life diesel exhaust exposure disrupts cortical lamina organization: Evidence for a reelin-related pathogenic pathway induced by interleukin-6.** *Brain Behav Immun* 2019, **78**:105-115. * This paper shows that perinatal exposure to DEP results in alterations of neuronal distribution within the cortical lamina, accompanied by upregulation of interleukin-6 and DNMT1, and decreased levels of reelin in adult mice. Since several polymorphisms of reelin are associated with Autism Spectrum Disorder (ASD) and reelin levels are low in ASD patients, such alterations are interpreted as the molecular substrates of the neurodevelopmental and behavioral effects of early life PM exposure.

47. Nawrot TS, Saenen ND, Schenk J, Janssen BG, Motta V, Tarantini L, Cox B, Lefebvre W, Vanpoucke C, Maggioni C, et al.: **Placental circadian pathway**

methylation and in utero exposure to fine particle air pollution. *Environ Int* 2018, **114**:231–241. * By combining the estimation of daily PM 2.5 exposure levels and the analysis of the methylation of CpG sites within the promoter regions of the Circadian pathway genes, the authors show that 3rd trimester PM 2.5 exposure is associated with placental Circadian pathway methylation.

48. Neven KY, Saenen ND, Tarantini L, Janssen BG, Lefebvre W, Vanpoucke C, Bollati V, Nawrot TS: **Placental promoter methylation of DNA repair genes and prenatal exposure to particulate air pollution: an ENVIRONAGE cohort study.** *Lancet Planet Heal* 2018, **2**:e174–e183. *By combining the estimation of daily exposure to different air pollutant and the analysis of the methylation of the promoter of key DNA repair and tumor suppressor genes, the authors show that PM2.5 exposure during pregnancy is associated with increased overall placental mutation rate and alterations in DNA repair gene methylation pattern.

49. Mckinnon PJ: **Maintaining genome stability in the nervous system.** *Nat Neurosci* 2013, **16**:1523-1529.

50. Bouchard-Cannon P, Mendoza-Viveros L, Yuen A, Kærn M, Cheng HYM: **The Circadian Molecular Clock Regulates Adult Hippocampal Neurogenesis by Controlling the Timing of Cell-Cycle Entry and Exit.** *Cell Rep* 2013, **5**:961-973.

51. Noda M, Iwamoto I, Tabata H, Yamagata T, Ito H, Nagata K ichi: **Role of Per3, a circadian clock gene, in embryonic development of mouse cerebral cortex.** *Sci Rep* 2019, **9**:5874.

437 **Acknowledgements**

438 We apologize to colleagues whose work we could not include due to space limitations. We
439 thank Dr. Sara Bonzano for precious help in figure graphics. Our work is supported by the
440 Individual funding for basic research (Ffabr) granted by the Italian Agency for the
441 Evaluation of University and Research, and local funds by University of Turin to EB. This
442 study was also supported by Ministero dell'Istruzione, dell'Università e della Ricerca—
443 MIUR project “Dipartimenti di Eccellenza 2018–2022” to Dept. of Neuroscience “Rita Levi
444 Montalcini”, University of Turin.

445

446 **Declaration of interests**

447 The authors declare no conflict of interest. The funding sponsors had no role in the
448 interpretation of data or in the writing of the manuscript.

449 **Figure legend**

450 **Figure 1. PM-induced alterations detected in the adult mouse brain following in-**
451 **utero or adult exposure.** Orange boxes (above) include the proposed underlying
452 mechanisms. BBB, blood-brain barrier; CC, corpus callosum; DG/SGZ, hippocampal
453 dentate gyrus/subgranular zone; EV, extracellular vesicles; NSCs, neural stem cells; OPC,
454 oligodendrocyte precursor cell; PM, particulate matter; PV, parvalbumin.

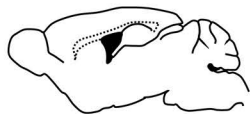
Microglia
& astrocyte
reactivity

BBB
breakdown

EV-associated
miRNAs

DNA methylation

In-utero PM exposure



Effects in young adults

CORTEX

- volume
- PV+ neurons
- proliferation



apoptosis
of neurons
and astrocytes

CC



OPC
expansion



OPC
maturation &
myelination

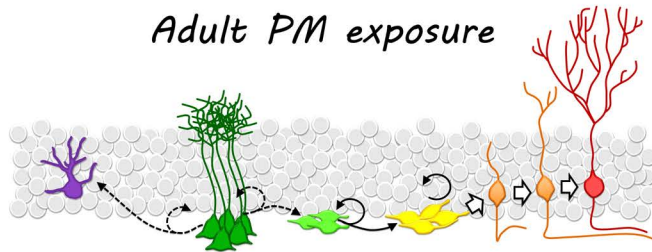
DG/SGZ

- proliferation
- dendritic
complexity



apoptosis
of neurons
and astrocytes

Adult PM exposure



NSCs/intermediate
progenitors:



proliferation

Unaltered
astrogliogenesis

Newborn neurons:

-survival



-acquisition of
mature markers

-dendritic
complexity